A Primer on the Orphan Drug Market:

Addressing the Needs of Patients with Rare Diseases

Wayne Winegarden, Ph.D.

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Introduction

Rare diseases are defined, in the U.S., as diseases that afflict less than 200,000 people. Although each particular rare disease only impacts a very small number of people, in total, there are approximately 6,000 to 8,000 diseases that have been categorized as rare.[1] Consequently, in total rare diseases afflict approximately seven percent of the U.S. population, or around 25 million people in the U.S. alone.[2] Therefore, the societal impact from rare diseases is large even though the impact from each rare disease is small.

The fundamental economic problem facing orphan drugs is scale. The average costs of developing an orphan drug is not less expensive than the average costs for developing non-orphan pharmaceutical drugs, but the potential population that can benefit is significantly smaller. And, the smaller potential population can actually increase developmental costs. For instance, fewer potential beneficiaries also imply fewer potential trial participants. Due to the relatively small proportion of the population that is afflicted by each rare disease, the investment incentives created by the ordinary patent system for pharmaceutical development are inadequate.

In response to this problem, Congress passed the Orphan Drug Act (ODA) in 1983. The ODA:

- Provided researchers who are the first to bring an orphan drug to market a seven-year market exclusivity for FDA-designated orphan drugs in addition to the current patent protections;
- Offered a tax credit equal to 50 percent of the expenditures during the clinical testing phase;
- Offered potential grants to help defray the research costs; and,
- Waived the FDA application fees.

ODA's goal was to increase the number of therapies available to people with rare diseases by improving the incentives to produce orphan drugs. Based on this criterion, ODA has been a success. The most oft-cited example of this success is the difference in orphan drug development pre-ODA compared to post-ODA. Between 1972 and 1983, the pre-ODA period, 10 new drugs were approved by the FDA to treat rare diseases. Between 1983 and 2010, the period following ODA's passage, 362 drugs to treat orphan diseases were approved.[3]

The societal impact from rare diseases is large even though the impact from each rare disease is small.

Since the passage of ODA, orphan drug development has also impacted mortality rates from rare diseases. In a 2001 analysis of the impact from new drugs on mortality from rare diseases and HIV, Dr. Frank Lichtenberg found:

> *Before the Orphan Drug Act went into effect (between 1979 and 1984), mortality from rare diseases grew at the same rate as mortality from other diseases. In contrast, during the next five years, mortality from rare diseases grew more slowly than mortality from other diseases. I estimate that one additional orphan drug approval in year t prevents 211 deaths in year t+1 and ultimately prevents 499 deaths, and that about 108 thousand deaths from rare diseases will ultimately be prevented by all of the 216 orphan drugs that have been approved since 1983.*[4]

Similarly, Yin (2008) found,

> *…that the ODA had a significant impact on rare disease drug development. I estimate that on average the ODA led to a 69 percent increase in the annual flow of new clinical trials for drugs for "traditional" long-established rare diseases. Innovation in the smallest markets was limited to an increase in the stock of drugs in the years immediately subsequent to the ODA's passage. This response*

> *likely represents final development of existing technologies. The impact on R&D for drugs treating rare diseases with higher prevalence was substantially larger in magnitude and sustained throughout the study period—an indication of greater innovative effort to develop novel technologies in response to the incentives.*
>
> *Overall, my results are consistent with Finkelstein (2004), who finds that policy-induced increases in expected demand for drugs in certain pharmaceutical classes were associated with increases in later stage clinical trials and final drug approvals. They are also consistent with Lichtenberg and Waldfogel (2003), who find that, after the ODA, the increase in the variety of drugs was higher for rare diseases than for non-rare diseases.* ***Results from the present study suggest that the ODA was able to increase both the stock and flow of R&D activity****. However, the differential impact of the ODA according to disease prevalence suggests that the effectiveness of tax credits on pharmaceutical R&D depends in part on revenue potential. Stimulating R&D in smaller markets may require larger tax credits or use of multiple incentives that affect investments on both cost and revenue margins.*[5] (Emphasis added)

Although ODA is generally viewed as a success,[6] problems with encouraging the development of orphan drugs remain, which have led to legislation, such as the TREAT Act, that would, among other issues, accelerate the review and approval processes for orphan drugs.[7]

Understanding ODA's success is important when evaluating the benefits created by orphan drug development. The historical evidence—the extreme differences between orphan drugs developed pre-ODA and post-ODA—illustrates that changing the drug development incentives is an effective policy that encourages the development of drugs to help patients suffering from rare diseases. The continued health threats created by rare diseases coupled with the continued economic problems created by the lack of scale warrant policies to continue improving the market incentives to develop orphan drugs.

Toward this end, this paper reviews the economics of the orphan drug market. The data illustrate that the benefits from continued orphan drug research outweigh the costs. Furthermore, while improvements can (and should) be made, the current public-private relationship creates an efficient division of labor. This relationship is defined by the government sector lowering certain government-created costs of drug development and providing researchers a longer period to recoup their development costs. These policies compensate for the problems of scale that limit the ability of researchers to sustainably engage in orphan drug research efforts. Consequently, private sector firms are capable of engaging in research on orphan drugs and attempt to help the 25 million Americans who are afflicted with a rare disease.

An Estimate of the Economic Costs from Rare Diseases—the Demand Side

Despite the large number of Americans impacted by rare diseases, there are few studies that document the economic impact from rare diseases. And, part of the reason is likely due to the obscure nature of the data. Obtaining a precise estimate of the total social costs from rare diseases is difficult—and is not the goal of this section. Leveraging a pivotal study by the Milken Institute (2007),[8] and confirming the healthcare cost portion of these estimates with government healthcare data, a reasonable approximation of the estimated social cost range from orphan diseases can be created. It is important to note upfront that this estimate is not precise, but is intended to generate an approximate economic cost estimate of rare diseases in the U.S.

Like other diseases, the economic impact from rare diseases can be broken down into direct costs and indirect costs. The direct costs include all relevant medical expenditures used in treating patients including medical treatment as well as costs expended for daily care (e.g., help feeding, dressing, etc.). Indirect costs include the loss in wages, benefits, and lost productivity that are attributed to the rare disease. Additionally, while difficult to measure, rare diseases also impose intangible costs on individuals and their families that are not economic, or quantifiable in dollar terms, but are no less real.

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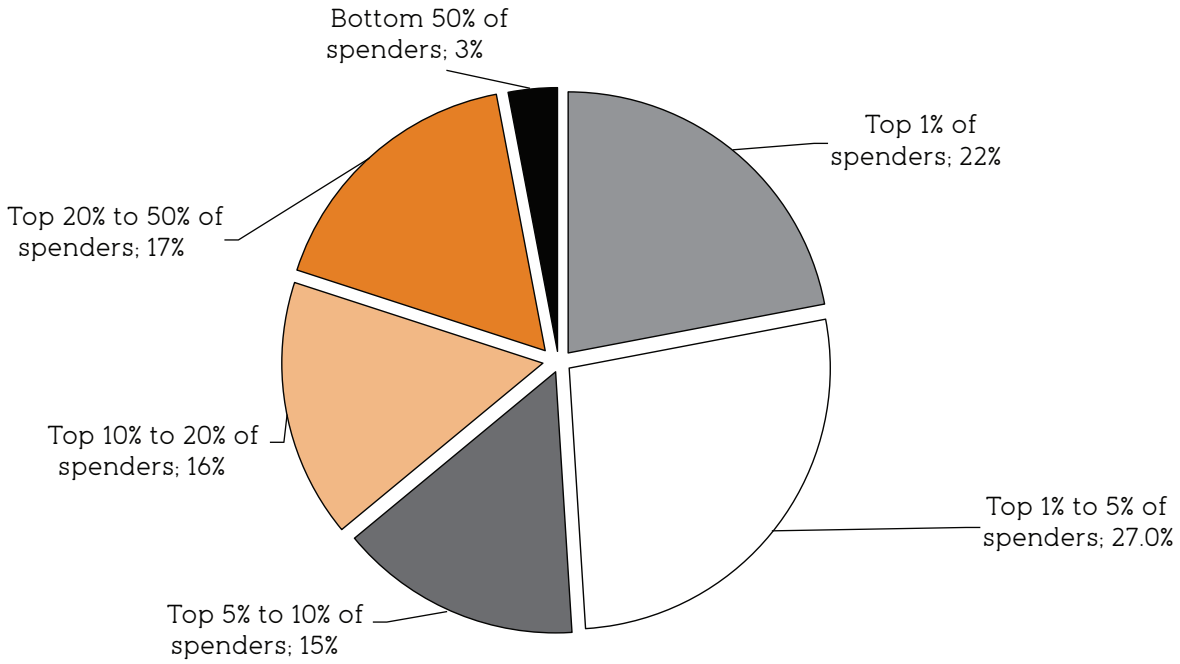
According to the National Health Expenditure Accounts (CMS) total national healthcare consumption expenditures in 2011 were $2.5 trillion.[9] Included in these expenditures were dental expenditures. While the evidence linking good dental health to good overall health is compelling, for conservative purposes we subtract the $105.7 billion spent on dental services in 2011 leaving a total national healthcare consumption expenditure estimate of $2.4 trillion. Based on an estimated U.S. population of 313.2 million, this equates to a per capita healthcare expenditure of $7,775 in 2011. If healthcare expenditures were equally distributed, which they are not, then the 25 million people afflicted with a rare disease would have spent $194.4 billion on healthcare in 2011.

But, healthcare expenditures are not distributed evenly across the population. As illustrated in Figure 1, 1 percent of the population was responsible for 22 percent of the total health care expenses as of 2002.

Figure 1
Percent of total health care expenses incurred by different percentiles of U.S. population 2002[10]



Furthermore, 50 percent of the population was responsible for 97 percent of the total health care expenses. While the data are from 2002, the historical evidence illustrates that this distribution of expenditures are relatively stable. According to the AHRQ:

> *From 1977 to 1996, the overall distribution of health care expenses among the U.S. population remained remarkably stable…, according to data from MEPS and its predecessor surveys. In 1977, the one percent of the population with the highest expenses accounted for 27 percent of all expenses, the top five percent accounted for 55 percent, and the bottom 50 percent accounted for three percent. However, the concentration of expenses at the top has decreased in recent years. The total expenses accounted for by the top one percent of spenders declined from 28 percent in 1996 to 22 percent in 2002, and the amount for the top five percent dropped from 55 to 49 percent in the same time period. The lower 50 percent of spenders remained at three to four percent of total expenditures during this period.*[11]

A 2012 AHRQ study confirms the continued skewed healthcare consumption expenditures: "in 2009, the top one percent accounted for 21.8 percent of the total expenditures with an annual mean expenditure of $90,061. The lower 50 percent of the population ranked by their expenditures accounted for only 3.1 percent and 2.9 percent of the total for 2008 and 2009 respectively."[12]

Assuming that those individuals suffering from a rare disease are in the top 50 percent of the population for expenditures but not in the top five percent, the estimated per capita healthcare expenditure for patients with rare diseases in 2011 is around $7,464—a bit lower than the simple per capita expenditure estimate. This estimate is also slightly lower than the estimated per capita expenditure for the top 50 percent of healthcare spenders of $7,980, which also incorporates the highest healthcare spenders.[13] Based on the estimated cost of $7,464, the total healthcare expenditures for people with rare diseases in 2011 was around $186.6 billion.

Extrapolations from a 2007 Milken Institute study are consistent with these estimates.[14] The Milken study estimates the total economic costs associated with seven common conditions (cancer (broken into several types), diabetes, hypertension, stroke, heart disease, pulmonary conditions, and mental disorders). The study found that:

> *The latest available information shows that in 2003, expenditures to treat the seven selected diseases totaled $277 billion for noninstitutionalized Americans. This is a conservative figure because it excludes the considerable health expenditures of the institutionalized population and because it excludes the spending associated with follow-on health consequences of the seven listed conditions. …*
>
> *The potential savings on treatment represents just the tip of the proverbial iceberg. Chronically ill workers take sick days, reducing the supply of labor—and, in the process, the GDP. When they do show up for work to avoid losing wages, they perform far below par—a circumstance known as "presenteeism," in contrast to absenteeism. Output loss (indirect impacts) due to presenteeism (lower productivity) is immense—several times greater than losses associated with absenteeism. Last (but hardly a footnote), avoidable illness diverts the productive capacity of caregivers, adding to the reduction in labor supply for other uses. Combined, the indirect impacts of these diseases totaled just over $1 trillion in 2003.*[15]

The Milken Institute's $1.3 trillion economic cost estimate covers seven of the most common chronic diseases. According to the Milken Institute there were a total of 109 million people with these chronic diseases in 2003. While not all rare diseases are chronic, the majority of rare diseases are genetic, and therefore chronic. Based on an estimated number of 25 million cases of chronic diseases in the U.S., and assuming similar costs for orphan and non-orphan drugs, the Milken Institute study would imply an estimated cost of $304.4 billion annually that is attributable to orphan diseases. Inflating the healthcare expenditures at the rate of overall healthcare expenditures and the economic costs at the overall inflation rate, in 2011 this figure would be approximately $391.8 billion: $97.4 billion in healthcare expenditures and $294.4 billion in economic costs.

Fifty percent of the population was responsible for 97 percent of the total health care expenses.

However, the Milken Institute estimates "exclude costs associated with the institutionalized population."[16] According to the Medical Expenditure Panel Survey (MEPS) website, these data (relied upon by the Milken Institute) "…provide[s] nationally representative estimates of health care use, health care expenditures, sources of payment, health insurance coverage, and health status for the U.S. civilian noninstitutionalized population."[17] The total MEPS expenditures equaled around 54 percent of the total National Health Care Expenditures estimated by CMS in 2009 (latest MEPS data available). Assuming proportionality in the institutionalized versus non-institutionalized populations, would imply a total medical cost for rare diseases from the Milken study of $180.1 billion—very similar to estimated costs based directly on the CMS data ($186.6 billion). Extrapolating from the Milken Institute study, consequently, implies an estimated total economic cost from rare diseases in the U.S. of around $474.5 billion.

Summing these estimates, the economic and social costs from rare diseases including current healthcare expenditures, loss of wages, and loss of productivity (quality of life issues are not included) are currently around $474.5 billion.

Orphan drugs can help reduce these costs—especially the economic costs—by increasing the ability of the medical profession to efficiently manage these rare diseases. For instance, Jessup (2012) reviewed the economics literature that examined the relationship between medical innovations, particularly pharmaceuticals, cost containments, and improved outcomes. Jessup found that "the economics literature generally indicates that innovation in medical products has produced tremendous benefits for the U.S. consumer in longer and healthier lives." PhRMA, summarizing a January 2010 *Health Affairs* analysis that examined the benefits from adhering to pharmaceutical regiments emphasized

> *…the importance of medication adherence to patients' health and overall treatment costs. The study, which focuses on four chronic conditions, found that patients who regularly adhered to their prescription regimen significantly reduced their total health care spending and lowered the number of emergency room visits and the number of days a patient spent in the hospital.*
>
> *"Across all four conditions, total health care costs were significantly lower for adherent patients, even after accounting for an increase in spending on medicines. Specifically, adherence reduced average annual health care spending by $7,823 for patients with congestive heart failure, $3,908 for hypertension, $3,756 for diabetes, and $1,258 in patients with dyslipidemia, according to the article.*

While the total economic cost estimates presented here are only indicative, they illustrate the tremendous health and economic costs created by rare diseases. The benefits gained by reducing these costs represent the value to consumers (demand) that orphan drugs can create.

The Costs Associated with Orphan Drug Development: Issues on the Supply-Side

Getting a new drug approved for sale, whether it is an orphan drug or non-orphan drug is a long process. While some differences between orphan drugs and non-orphan drugs exist (e.g., orphan drugs may require more time during the clinical trial stages but, due to FDA preferences, slightly shorter regulatory approval times), overall the development times and processes are similar. What is dis-similar, as discussed above, is the small potential market for orphan drugs. Reviewing the typical costs associated with developing a new drug, coupled with the small potential market for orphan drugs, illustrate the necessity for ODA type policies.

The drug development process requires a long-run commitment by a firm and its investors. On average, it takes 10–15 years to move a potential new drug (orphan, or non-orphan) from the research stage to a treatment approved by the Food and Drug Administration (FDA), assuming that the drug is approved by the FDA, an achievement only a minority of drugs will ever reach.[18]

The FDA in the U.S. requires pharmaceutical manufacturers to demonstrate the safety and effectiveness of

their proposed new drugs. Safety and effectiveness standards typically include pre-clinical trials, clinical trials, submitting proprietary manufacturing data, as well as paying for both the direct costs of these tests and any relevant government fees.

Throughout the entire development process, the manufacturing firm must invest more and more resources into the research and development each and every year. These costs are not offset by any revenues as long as the drug is not approved for use by the regulator. Consequently, the drug development process requires investors to part with progressively larger amounts of their own capital without any compensation. In total, the cost to develop one successful drug, incorporating the costs of failure, is $1.2 billion.[19] And, this estimate may be low. Citing a study by Bernard Munos of the Innothink Center, Herper (2012) noted that adjusting the $1.2 billion:

> *estimate for current failure rates results in an estimate of $4 billion in research dollars spent for every drug that is approved. But Munos showed me another figure, where he divided each drug company's R&D budget by the average number of drugs approved. This was far more dramatic.*
>
> *Wanting to make this even more rigorous, Forbes…took Munos' count of drug approvals for the major pharmas and combined it with their research and development spending as reported in annual earnings filings going back fifteen years, pulled from a Thomson Reuters database using FactSet. We adjusted all the figures for inflation. Using both drug approvals and research budgets since 1997 keeps the estimates being skewed by short-term periods when R&D budgets or drug approvals changed dramatically.*
>
> *The range of money spent is stunning. AstraZeneca has spent $12 billion in research money for every new drug approved, as much as the top-selling medicine ever generated in annual sales; Amgen spent just $3.7 billion. At $12 billion per drug, inventing medicines is a pretty unsustainable business. At $3.7 billion, you might just be able to make money (a new medicine can probably keep generating revenue for ten years; invent one a year at that rate and you'll do well).*
>
> *There are lots of expenses here. A single clinical trial can cost $100 million at the high end, and the combined cost of manufacturing and clinical testing for some drugs has added up to $1 billion. But the main expense is failure. AstraZeneca does badly by this measure because it has had so few new drugs hit the market. Eli Lilly spent roughly the same amount on R&D, but got twice as many new medicines approved over that 15 year period, and so spent just $4.5 billion per drug.*[20]

There are also often overlooked regulatory expenses. More and more, products require intellectual property right protection from illegal knock-offs. These include protecting the rights of clothes designers from cheap imitations or protecting the rights of artists to not have their music sold without being paid the royalties that are due to them. For pharmaceuticals, this means full respect for the patents the manufacturers have earned over the drugs they have created. It is important to note that simply giving and enforcing the pharmaceuticals patent rights will not eliminate cheating, illegal copying, black markets, and knock-offs. It does give the manufacturer a legal recourse against such activities when and if they arise. Such recourse is not without costs, which also need to be factored into the products cost structure.

In light of these high development costs, the key question for patented drug manufacturers (both orphan and non-orphan drugs) is how to determine whether this tremendous resource investment will be worthwhile. If the present value of the expected revenues from a successful drug exceeds the present value of the expected costs, with enough compensation for the risk the investor has to bear, then it is worthwhile to undertake the investment.

But, timing is everything. Receiving one-dollar next year is not as good as receiving one-dollar today. The present value of a future dollar is worth less than a current dollar depending upon the time value of money and the length of the wait. Using this same logic, the timing of the drug development process requires the manufacturer to invest the costs up front but only receive the revenues later in time. The future revenue streams must be significantly large to compensate for the current development costs.

The prospects of success for a new drug must be enough to make the investment of time and resources worthwhile. The manufacturer must estimate expected costs and revenues. Calculating expected revenues requires judgments regarding the potential market just like a manufacturer of any new product. Such considerations include the expected number of people that would use the product, the competitive products available as well as whether consumers would be willing and able to spend the necessary amount of money to make the investment worthwhile. Putting these constraints together, the manufacturer would only engage in the R&D process if both the probability for success is high enough and the discounted value of the expected costs are such that the expected revenues exceed these costs.

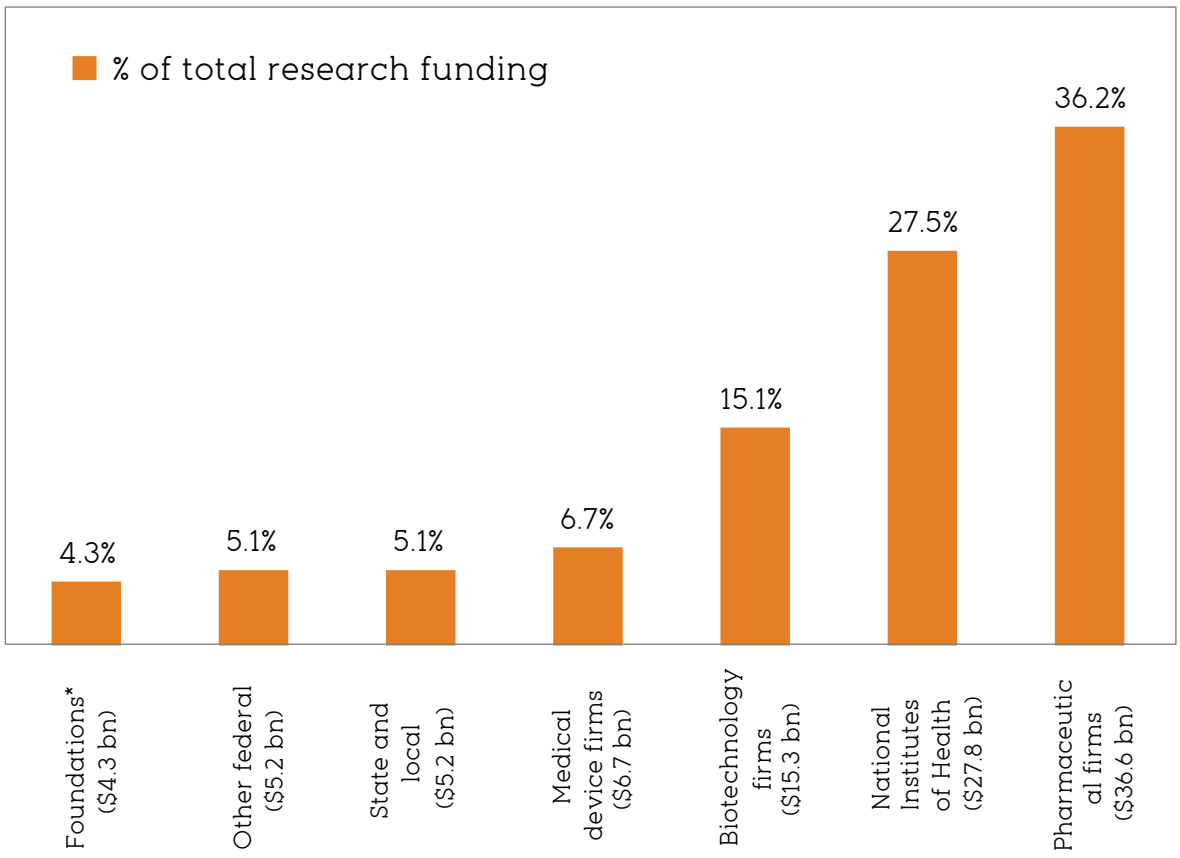
More and more, products require intellectual property right protection from illegal knock-offs.

What does all of this mean for a pharmaceutical manufacturer debating whether to engage in the lengthy R&D process? Beyond the pure market considerations, the manufacturers must consider the regulatory responses. These include the expected length of time for regulatory approval of the drug, the number of expected years in which the manufacturer has exclusive selling rights, and the likelihood that the government has the will and capability to enforce the manufacturer's exclusive selling rights from copycat manufacturers as well as abstain from government imposed price controls. The regulatory concerns will have the effect of either raising the expected production costs, as is the case for an unjustifiably burdensome regulatory approval process, or lowering the expected revenues, as is the case with price controls. After factoring in all of these considerations, if the expected revenues still exceed expected costs, allowing for a high enough rate of return, then it is worthwhile to undertake the project.

In the case of orphan drugs, the ODA has lowered the regulatory costs and increased the expected revenues by lengthening the time available to recoup the financial investment. These supply-side incentives have been crucial in expanding the number of orphan drugs available to treat rare diseases and address the still high economic burden associated with rare diseases. According to the Office of Management and Budget (OMB), the tax credit for orphan drug research provided tax relief of $770 million in 2011, and is estimated to be $930 million in 2012.[21] By 2016, OMB estimates the tax credit will provide a bit under $2 billion in tax relief. Additionally, "Within FDA, the FY 2010 budget for the Office of Orphan Products Development is $22.1 million, including $15.2 million for the orphan products grants, $3 million for the pediatric device consortia grants, and $3.8 million for program administration including salaries and program operations."[22]

In the case of drug development there are complimentary investments being made through the public sector and private foundations (NIH funding, etc.). The costs of developing orphan drugs are intertwined with the amount and direction of the complimentary investments that are made through these institutions. But, compared to the public expenditures, private firms are still the major investors. According to Field and Boat (2011) pharmaceutical companies and other private sector firms invested $58.6 billion in R&D in 2007 or 58 percent of total R&D expenditures that year, see Figure 2.[23] If private charities are included, the private sector invested $62.9 billion or 62.3 percent of total R&D expenditures that year. And, these estimates could be low. For instance, the Field and Boat (2011) estimates show that pharmaceutical firms invested $36.6 billion in 2007. According to PhRMA, total pharmaceutical investment in R&D was $47.9 billion in 2007 and estimated to be $49.5 billion in 2011.[24]

Figure 2
Funding for Biomedical Research in the U.S.
2007[25]

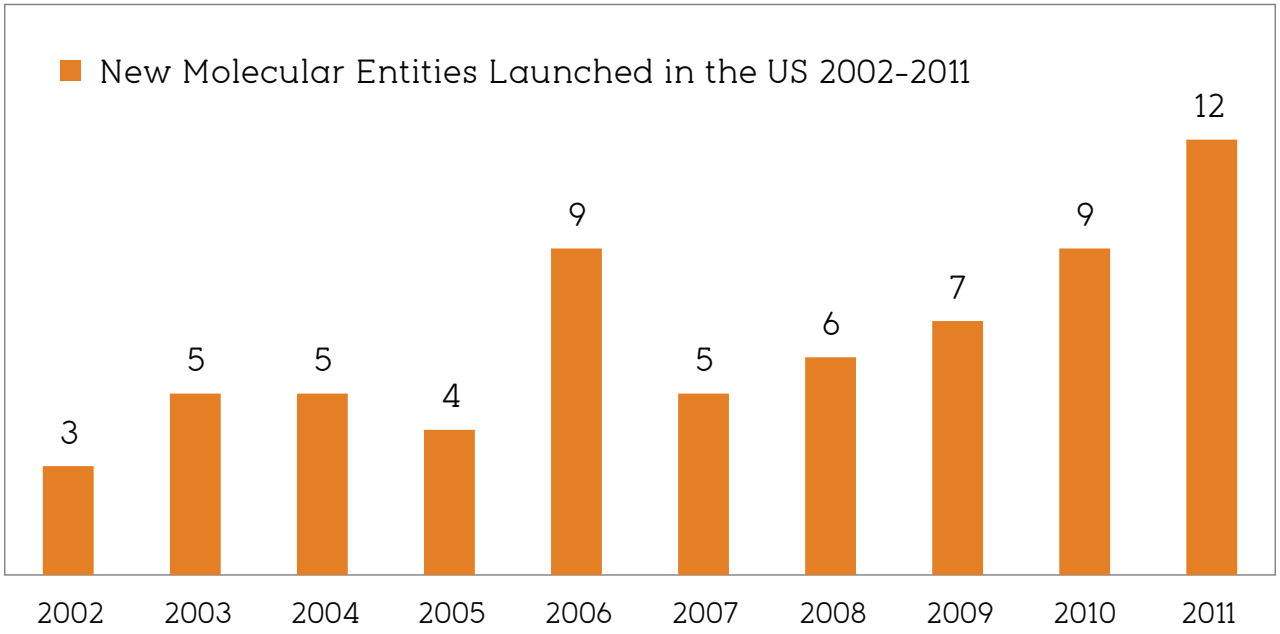


The Orphan Drug Market

All markets are defined by its demand and supply attributes. The orphan drug market is defined by the costs, benefits, and constraints as defined above. The demand-side of the market is the 25 million Americans (patients) who are afflicted with a rare disease that could benefit from orphan drugs—suffering with approximately $475 billion in economic and health costs. The supply-side of the market is the pharmaceutical companies that can create and provide these drugs to the patients afflicted with a rare disease, but face a long, uncertain, and costly drug development process if the companies are going to be capable of providing the new orphan drugs to the consumers who can benefit. Because it is the healthcare market, the connection between the customers (demand side) and manufacturers (supply side) also must accommodate medical professionals, insurance companies, and government agencies.

The orphan drug market has grown significantly along with the growth in new orphan drug approvals. Figure 3 details the total number of New Molecular Entities (NME) launched in the U.S. over the past 10 years.

Figure 3
New Molecular Entities, Orphan Drugs Launched in the U.S., 2002 - 2011[26]



Not only has there been a steady stream of new NME's designed to address rare diseases, 2011 saw the highest number of new NME launches in the past 10 years. These results are consistent with the overall introduction of NME's during the post-ODA period.[27] Additionally, the "important breakthroughs for rare orphan diseases, that afflict less than 200,000 people, transformed disease treatment options through personalized medicines based on specific genetic markers for subtypes of cancer and individually cultured immunotherapies."[28]

The total spending on pharmaceutical drugs in 2011 in the U.S. was $320 billion.[29] Globally, total spending on pharmaceutical drugs was approximately $880 billion in 2011.[30] Total global spending on orphan drugs is estimated to be between $50 billion and $85 billion or between 5.7 percent and 9.7 percent of total global pharmaceutical spending.[31]

The orphan drug market is also growing fast. According to *Reuters*, "The compound annual growth rate (CAGR) of the orphan drug market between 2001 and 2010 was an impressive 25.8 percent, compared to only 20.1 percent for a matched control group of non-orphan drugs. These data, combined with the increasing number of orphan drug approvals, suggests that the CAGR of launched orphan drugs will outshine that of the non-orphan control drugs over the next 30 years."[32]

The market data confirm two important developing trends in the orphan drug market:

- There is a real, and growing, market need for orphan drugs; and,
- Under the current policy environment, pharmaceutical firms are able to effectively develop

orphan drugs to address these needs.

Conclusion

Drug development is a long and risky process. The development of orphan drugs, because they serve patients with rare diseases, face additional economic obstacles created by the lack of scale. Despite the more difficult economics of serving patients with rare diseases, orphan drug development is desperately needed.

The incentives created by Congress in passing the Orphan Drug Act of 1983 made significant changes to the policy environment. These changes helped make research and production of orphan drugs possible, empowering the private sector to serve this market. In response, orphan drug development has become a significant area of investment for pharmaceutical companies which, along with other private investors, are now driving the current therapeutic drug research efforts.

The "back of the envelope" calculations presented above illustrates that the total economic cost from all rare diseases in the U.S. could be in the hundreds of billions of dollars. The annual sales of orphan drugs (i.e., the value provided to current patients) are currently around $50 billion to $85 billion. To a large extent, this value was enabled by lowering the costs imposed on private sector pharmaceutical research created by government regulations.

Despite the more difficult economics of serving patients with rare diseases, orphan drug development is desperately needed.

Endnotes

1 Wayne H. Winegarden, Ph.D. is a Senior Fellow with the Pacific Research Institute, a Partner in the economic consulting firm Arduin, Laffer & Moore Econometrics, and a contributor to EconoSTATS at George Mason University.

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About the Author

WAYNE WINEGARDEN, PH.D.

Wayne Winegarden has more than 20 years of experience in public policy, economic research, and business. His expertise lies in applying quantitative and macroeconomic analysis to create greater insights for policy leaders, and corporate strategy and planning for decision makers. He has advised Fortune 500 companies, state legislators, political candidates, as well as small business and trade associations. He founded Economic Solutions and Laffer Associates strategy services; managing staff, budget, and corporate development.

Currently, he is Partner at Arduin, Laffer & Moore Econometrics, which advises federal, state, & municipal leaders, political candidates, and private sector clients, on economic, fiscal and state policies. The firm analyzes the impacts of policy upon markets, identify trends and opportunities, and inform strategy that optimizes performance.

Prior to Arduin, Laffer & Moore Econometrics, Dr. Winegarden was a managing director at Laffer Associates from 2008 to 2012. He was also a manager at Philip Morris International and Philip Morris Management Corporation where he analyzed economic and fiscal issues. His teaching experience includes Marymount University and George Mason University.

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